REMARKS/ARGUMENTS

Claims 1-18 are pending in the instant application. The bases for the Examiner's rejection of claims 1-18 are addressed below.

The Applicants respectfully acknowledge the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned as the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a). The Applicants confirm that the subject matter of the instant claims were commonly owned at the time the inventions were made.

35 U.S.C. § 103(a) Rejections Overcome

I. Sullivan *et al.*, in view of Hardman, and view of DiPiro *et al.*, and in further view of Solomons and McMurry

The Examiner has rejected pending claim 1 and claims 4-8 under 35 U.S.C. § 103(a), alleging the claims as obvious in view of the teachings of the references cited above. (Office Action at ¶7). Claim 1 and claims 4-8 are directed to a method of treating or ameliorating hypertension in individuals in need thereof which is comprised of orally administering an effective amount of HCA or derivatives thereof, including the metal salts, amides or esters. The Examiner concludes that the references cited above make obvious the instantly claimed subject matter based on the following observations: (1) hydroxycitrate (HCA) has been experimentally shown to reduce obesity and cholesterol synthesis (Office Action at ¶8; Sullivan *et al.*); (2) obesity was known at the time of the instant application to be positively correlated with hypertension (Office Action at ¶8, Hardman); (3) aggressive dietary programs have been shown to reduce cardiovascular events in high-risk groups (Office Action at ¶9); (4) hypertensive subjects with moderately elevated serum cholesterol have a greater risk of coronary heart disease (Office Action at ¶9); (5) one of skill in the art could convert between HCA and its conjugate base (Office action at ¶10); (6) while Sullivan *et al.* is silent with regard to the lactone form of HCA, it was widely accepted that carboxylic acids like HCA "readily" cyclize to form lactone (Office Action at ¶10; Solomons); (7) carboxylic acid can be readily converted to other carboxylic acid derivatives (Office Action at ¶10; McMurry); (8) one of skill in the art could readily convert HCA into its corresponding ester and/or amide derivatives for the purpose of generating a controlled-release for of HCA (Office Action at ¶10); (9) although Sullivan *et al.*

teaches the use of sodium salt of HCA one of skill in the art could readily substitute one pharmaceutically acceptable cation for another (Office Action at ¶10); and determination of a dosage having the optimum therapeutic index is well within the level of the one of ordinary skill and the artisan would be motivated to determine optimum amounts for administration (Office Action at ¶10).

Claim 1 and claims 4-8 do not fail for obviousness in view of Sullivan *et al.*, in view of Hardman, in view of DiPiro *et al.*, and in further view of Solomons and McMurry within the meaning of 35 U.S.C. § 103(a). As detailed in Section 2142 of the Manual of Patent Examination and Procedure, to establish *prima facie* obviousness under 35 U.S.C. § 103 three criteria must be met. These criteria are as follows:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2142.

"To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). In the instant case, the references recited above do not expressly suggest a method of treating or ameliorating hypertension in individuals in need thereof which is comprised of orally administering an effective amount of HCA or derivatives thereof, including the metal salts, amides or esters. As such, to sustain the rejection of the claimed subject matter under 35 U.S.C. § 103, the references, when viewed as a whole, must "impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

The Examiner concludes that the references cited above make obvious the instantly claimed subject matter based, in part, on the following observations: (1) HCA has been experimentally shown to reduce obesity and cholesterol synthesis (Office Action at ¶8; Sullivan *et al.*); (2) obesity was known at the time of the instant application to be positively correlated

with hypertension (Office Action at ¶8, Hardman); (3) aggressive dietary programs have been shown to reduce cardiovascular events in high-risk groups (Office Action at ¶9); and (4) hypertensive subjects with moderately elevated serum cholesterol have a greater risk of coronary heart disease (Office Action at ¶9). The Examiner's analysis is not convincing, however, because this reasoning rests on a fundamental assumption that a composition which elicits weight loss in an obese subject is, *a priori*, effective to reduce hypertension. This assumption is not supported in the art relating to drug therapy for the treatment of obesity. Indeed, many methods used to treat obesity can elevate blood pressure, *e.g.*, ephedrine, phentermine, Meridia (sibutramine), *etc.*, and, in some cases, is contraindicated for use in hypertensive subjects. Dickerson *et al.*, *Am Fam Physician* 2000;61:2131-8,2143; Cerulli *et al.*, *Ann Pharmacother* 1998;32:88-102; .Wooltorton, *CMAJ* May 14, 2002; 166 (10). As such, the references cited above, when viewed as a whole, would not imply to one of ordinary skill in the art that a method employing HCA would treat or ameliorate hypertension in a subject. That is, it is not implied in the references cited above or clear from the Examiner's reasoning that the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. To the contrary, the art would suggest that it is unpredictable whether the administration of a composition associated with weight loss in a subject, *e.g.*, HCA, would result in lower blood pressure in the hypertensive subject. In light of this unpredictability, one of ordinary skill in the art would not necessarily have had any reasonable expectation of success in reducing hypertension by administering HCA to a subject based on the teachings of the references cited about.

There are multiple sources for a motivation to combine references, yet the Office impermissibly relies on the level of skill of the ordinary artisan to provide the motivation to combine the references cited above. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). It is settled that the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Indeed, the Examiner states that, "the determination of a dosage having the optimum therapeutic index, which includes pharmaceutically acceptable salts, is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect if the drug while minimizing adverse and/or unwanted side-effects. Accordingly, these references make obvious the instantly claimed subject matter." (Office Action at ¶10; page 5, lines 15-20).

The Applicants traverse the rejection under 35 U.S.C. §103 for obviousness of the claimed subject matter in light of Sullivan *et al.*, in view of Hardman, and view of DiPiro *et al.*, and in further view of Solomons and McMurry because the Office has failed to meet its burden to support the conclusion that the claimed invention is directed to obvious subject matter as the teachings of Sullivan *et al.*, in view of Hardman, and in view of DiPiro *et al.* do not expressly or impliedly suggest the claimed invention and the Examiner has not presented a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. Based on the unpredictable characteristics of anorectic compositions in the analogous art, there was no reasonable basis to expect that the administration of a composition associated with weight loss in a subject, *e.g.*, HCA, would result in lowered blood pressure in the hypertensive subject. Furthermore, the Office impermissibly relies on the level of skill of the ordinary artisan to provide the motivation to combine the references cited above. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §103 rejections.

II. Sullivan *et al.*, in view of Hardman, and in view of DiPiro *et al.* and in further view of Solomons and McMurry

The Examiner has rejected pending claims 1-18 under 35 U.S.C. § 103(a), alleging the claims as obvious in view of the teachings of the references cited above. (Office Action at ¶11) Claim 1 and claims 4-8 are directed to a method of treating or ameliorating hypertension in individuals in need thereof which is comprised of orally administering an effective amount of HCA or derivatives thereof, including the metal salts, amides or esters. Claim 2 and claims 9-13 are directed to a method of treating or ameliorating hypertension by lowering elevated insulin in individuals in need thereof which is comprised of orally administering an effective amount of HCA or derivatives thereof, including the metal salts, amides or esters. Claim 3 and claims 14-18 are directed to a method of treating or ameliorating hypertension by lowering elevated glucocorticoids in individuals in need thereof which is comprised of orally administering an effective amount of HCA or derivatives thereof, including the metal salts, amides or esters. The Examiner concludes that the references cited above make obvious the instantly subject matter of claims 1-18 of the instant application based on the following observations: (1) hydroxycitrate (HCA) has been experimentally shown to reduce obesity and cholesterol synthesis (Office Action at ¶12; Sullivan *et al.*); (2) *in vivo* rat models of obese rats had reduced food intake and body weight gain with administration of HCA (Office Action at ¶12; Sullivan *et al.*); (2) obesity

was known at the time of the instant application to be positively correlated with hypertension (Office Action at ¶12, Hardman); (3) aggressive dietary programs have been shown to reduce cardiovascular events in high-risk groups (Office Action at ¶13); (4) hypertensive subjects with moderately elevated serum cholesterol have a greater risk of coronary heart disease (Office Action at ¶13; DiPiro *et al.*); (6) body weight and obesity are common characteristics of diabetes (Office action at ¶14; DiPiro *et al.*); (7) DiPiro *et al.* teaches various causes of diabetes, *inter alia*, elevated insulin an glucocorticoids and hormones (Office Action at ¶14; DiPiro *et al.*); (8) treating hypertension as well as diabetes with the administration of HCA or an analog thereof to an individual in need thereof, the individual would also be treating diabetes by *inter alia*, controlling the weight of the individual and also by lowering glucose levels as well as insulin and other hormones (Office Action at ¶14; see DiPiro *et al.*); (9) in view of *In re Swinehart*, lowering elevated insulin and elevated glucocorticoid levels is an inherent process that already occurs with the administration of HCA to treat obesity and hypertension in the prior art (Office Action at ¶14; *In re Swinehart*, 169 U.S.P.Q. 226; Sullivan *et al.*, in view of Hardman); (10) it would have been obvious to the skilled artisan to utilize analogs of HCA to treat hypertension (Office Action at ¶15); (11) the lowering of insulin and glucocorticoids is an inherent biochemical mechanism that already occurs with the administration of HCA as well as its analogs (Office Action at ¶15); (12) it would have been obvious, if not inherent, to the skilled artisan that by treating an individual with HCA, glucose, insulin and other hormone levels could be modified and manipulated especially since it is known to treat obesity (Office Action at ¶15); (13) one of skill in the art could convert between HCA and its conjugate base (Office action at ¶16); (14) while Sullivan *et al.* is silent with regard to the lactone form of HCA it was widely accepted that carboxylic acids like HCA "readily" cyclize to form lactone (Office Action at ¶16; Solomons); (15) carboxylic acid can be readily converted to other carboxylic acid derivatives (Office Action at ¶16; McMurry); (16) one of skill in the art could readily convert HCA into its corresponding ester and/or amide derivatives for the purpose of generating a controlled-release for of HCA (Office Action at ¶16); (17) although Sullivan *et al.* teaches the use of sodium salt of HCA one of skill in the art could readily substitute one pharmaceutically acceptable cation for another (Office Action at ¶16); and determination of a dosage having the optimum therapeutic index is well within the level of the one of ordinary skill and the artisan would be motivated to determine optimum amounts for administration (Office Action at ¶16).

For all the reasons cited in Section I above, claim 1 and claims 4-8 do not fail for obviousness in view of Sullivan *et al.*, in view of Hardman, in view of DiPiro *et al.*, and in further view of Solomons and McMurry within the meaning of 35 U.S.C. §103(a). The observations and recitations noted above do not cure the failure of the Office to meet its burden to support the conclusion that the claimed invention is directed to obvious subject matter as the teachings of Sullivan *et al.*, in view of Hardman, and in view of DiPiro *et al.*, do not expressly or impliedly suggest the claimed invention and the Examiner has not presented a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §103 rejections with respect to claim 1 and claims 4-8.

Claim 2 and claims 9-13 do not fail for obviousness in view of Sullivan *et al.*, in view of Hardman, in view of DiPiro *et al.*, and in further view of Solomons and McMurry within the meaning of 35 U.S.C. § 103(a). "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). In the instant case, the references recited above do not expressly suggest a method of treating or ameliorating hypertension by lowering elevated insulin in individuals in need thereof which is comprised of orally administering an effective amount of HCA or derivatives thereof, including the metal salts, amides or esters. As such, to sustain the rejection of the claimed subject matter under 35 U.S.C. § 103, the references, when viewed as a whole, must "impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

The Examiner concludes that the references cited above make obvious the instantly claimed subject matter based, in part, on the following observations: (1) body weight and obesity are common characteristics of diabetes (Office action at ¶14; DiPiro *et al.*); (2) DiPiro *et al.* teaches various causes of diabetes, *inter alia*, elevated insulin and glucocorticoids and hormones (Office Action at ¶14; DiPiro *et al.*); (3) treating hypertension as well as diabetes with the administration of HCA or an analog thereof to an individual in need thereof, the individual

would also be treating diabetes by *inter alia*, controlling the weight of the individual and also by lowering glucose levels as well as insulin and other hormones (Office Action at ¶14; see DiPiro *et al.*); and (4) in view of *In re Swinehart*, lowering elevated insulin and elevated glucocorticoid levels is an inherent process that already occurs with the administration of HCA to treat obesity and hypertension in the prior art (Office Action at ¶14; *In re Swinehart*, 169 U.S.P.Q. 226; Sullivan *et al.*, in view of Hardman). The Examiner's analysis is not convincing as the reasoning as to why the artisan would have found the claimed invention obvious in light of the teachings of the references is lacking. For example, the Examiner generally notes that "body weight and obesity are common characteristics of diabetes" (Office Action at ¶14; reference to unspecified material in DiPiro *et al.*). Then Examiner then states that, "[a]ccordingly, by treating hypertension as well as obesity with the administration of (-) hydroxycitrate or an analog thereof to an individual in need thereof, the individual would also be treating diabetes by *inter alia*, controlling the weight of the individual and also by lowering glucose levels as well as insulin and other hormones." (Office Action at ¶14, reference to unspecified material in DiPiro *et al.*). That is, the logical connection, as well as, support for the logic being applied by the Examiner, between the observation that body weight and obesity are common characteristics of diabetes and the apparent conclusion that "by treating hypertension as well as obesity with the administration of (-)-hydroxycitrate or an analog thereof to an individual in need thereof, the individual would also be treating diabetes by *inter alia*, controlling the weight of the individual and also by lowering glucose levels as well as insulin and other hormones" is illusory. (Office Action at ¶14) As noted above, claim 2 and claims 9-13 are directed to a method of treating or ameliorating hypertension by lowering elevated insulin in individuals in need thereof which is comprised of orally administering an effective amount of HCA or derivatives thereof, including the metal salts, amides or esters. The claim is not restricted to the treatment of hypertension in diabetic individuals. Furthermore, adverse metabolic effects have been associated with compositions used in the therapy of hypertension, especially diuretics and beta-blockers. These effects include electrolyte, glucose/insulin, lipid and uric acid disturbances. For example, both diuretics and beta-blockers, especially nonselective beta-blockers that lack intrinsic sympathomimetic capabilities, have been associated with disturbances in glucose/insulin metabolism and can cause deleterious alterations in the profile of circulating plasma lipids. (Preuss *et al.*, *Drug Saf.* 1996 Jun;14(6):355-64.). Also, *Gymnema sylvestre*, an Indian herb touted to reduce blood sugar levels and treat diabetes, in animal experiments raised blood

pressure. (Preuss HG, *et al.*, *J Am Coll Nutr.* 1998 Apr;17(2):116-23.). As such, the references cited above, when viewed as a whole, would not imply to one of ordinary skill in the art that HCA would be useful to treat or ameliorate hypertension by reducing insulin level in a subject. That is, it is not implied in the referenced cited above or clear from the Examiner's reasoning that the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.

Claim 3 and claims 14-18 do not fail for obviousness in view of Sullivan *et al.*, in view of Hardman, in view of DiPiro *et al.*, and in further view of Solomons and McMurry within the meaning of 35 U.S.C. § 103(a). The Office appears to offer essentially the same reasoning for the rejection of claim 3 and claims 14-18 as described above for the rejection of claim 2 and claims 9-13. For the reasons stated above the Examiner's analysis is not convincing as the reasoning as to why the artisan would have found the claimed invention obvious in light of the teachings of the references is lacking. That is, the logical connection, as well as, support for the logic being applied by the Examiner, between the observation that body weight and obesity are common characteristics of diabetes and the apparent conclusion that by treating hypertension as well as obesity with the administration of (-)-hydroxycitrate or an analog thereof to an individual in need thereof, the individual would also be treating diabetes by *inter alia*, controlling the weight of the individual and also by lowering glucose levels as well as insulin and other hormones" is illusory. (Office Action at ¶14). As noted above, claim 3 and claims 14-18 are directed to a method of treating or ameliorating hypertension by lowering elevated glucocorticoid level in individuals in need thereof which is comprised of orally administering an effective amount of HCA or derivatives thereof, including the metal salts, amides or esters. The claim is not restricted to the treatment of hypertension in diabetic individuals. Furthermore, treatment of elevated glucoocorticoids in a subject is not, *inter alia*, treatment of hypertension. To the contrary, some compounds used to treat elevated glucocorticoid levels actually either worsen or even induce hypertension. For example, RU-486 (Mifepristone), the French abortion pill and anti-glucocorticoid, unexpectedly raises blood pressure in some subjects. (Opoku *et al.*, Acta Endocrinol (Copenh), 1992 Sep;127(3):258-61). That is, it is not implied in the referenced cited above or clear from the Examiner's reasoning that the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.

The Office also predicates part of its analysis for rejection of claims 1-18 under 35 U.S.C. § 103 in view of the holding in *In re Swinehart*, and also concludes that lowering elevated

insulin and elevated glucocorticoid levels is an inherent process that already occurs with the administration of HCA to treat obesity and hypertension in the prior art (Office Action at ¶14; *In re Swinehart*, 169 U.S.P.Q. 226; Sullivan *et al.*, in view of Hardman). It is noteworthy that the Office quotes the holding of *In re Swinehart*, 169 U.S.PQ. 226 as stating, "a newly discovered property does not necessarily mean that the product is unobvious, since this property may be inherent in the prior art." (Office Action at ¶14). Applicants respectfully submit that the quoted language could not be found in *In re Swinehart*. Also, the instant case is distinguished from *In re Swinehart* which presents its analysis in the context of claims rejected under 35 U.S.C. § 112, not claims rejected under 35 U.S.C. § 103 as in the instant Office Action. Also, *In re Swinehart* is not persuasive in light of more recent precedent in *Jansen v. Rexall Sundown* (342 F.3d 1329, 68 U.S.P.Q.2d (BNA) 1154 (Fed. Cir. 2003)). The *Jansen* Court distinguished a method claim of use over an allegedly infringing use by construing the claimed method as limited to achieve a particular objective. *Jansen* stands for the precedent "that a method of using an old composition may be patentable simply by reciting a new property of the composition or a different purpose for using it." Kelly, D.A., 21 *Santa Clara Computer & High Tech L.J.* 319, 322 (2005). Like the method claims of *Jansen*, claims 1-18 of the instant application are directed to the use of a known composition wherein the method is limited to "individuals in need thereof." *Jansen,* 342 F.3d 1330. Thus, as in *Jansen*, the instant claims should be construed to mean that administration of HCA for some purpose other than treating or ameliorating hypertension is not practicing the claimed invention. *Jansen*, 342 F.3d at 1334. It follows that the use of HCA to treat obesity is patentably distinct from the use of HCA to treat or ameliorate hypertension and does not anticipate the subject matter claimed in the instant case. As such the references cited above, when considered as a whole to not render claims 1-18 of the instant case unpatentable for obviousness within the meaning of 354 U.S.C. § 103.

There are multiple sources for a motivation to combine references, yet the Office impermissibly relies on the level of skill of the ordinary artisan to provide the motivation to combine the references cited above. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). It is settled that the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Indeed, the Examiner states that, "the determination of a dosage having the optimum therapeutic index, which includes pharmaceutically acceptable salts, is well within the level of one having ordinary skill in the art, and the artisan would be

motivated to determine optimum amounts to get the maximum effect if the drug while minimizing adverse and/or unwanted side-effects. Accordingly, these references make obvious the instantly claimed subject matter." (Office Action at ¶16; page 9, lines 1-6).

The Applicants traverse the rejection under 35 U.S.C. §103 for obviousness of the claimed subject matter in light of Sullivan *et al.*, in view of Hardman, and view of DiPiro *et al.*, and in further view of Solomons and McMurry because the Office has failed to meet its burden to support the conclusion that the claimed invention is directed to obvious subject matter as the teachings of Sullivan *et al.*, in view of Hardman, and in view of DiPiro *et al.* do not expressly or impliedly suggest the claimed invention and the Examiner has not presented a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. Based on the unpredictable characteristics of anorectic compositions in the analogous art, there was no reasonable basis to expect that the administration of a composition associated with weight loss in a subject, *e.g.*, HCA, would result in lowered blood pressure in the hypertensive subject. Furthermore, the Office impermissibly relies on the level of skill of the ordinary artisan to provide the motivation to combine the references cited above. Moreover, as in *Jansen*, the instant claims should be construed to mean that administration of HCA for some purpose other than treating or ameliorating hypertension is not practicing the claimed invention. *Jansen*, 342 F.3d at 1334, 68 U.S.P.Q at 1158. It follows that the use of HCA to treat obesity is patentably distinct from the use of HCA to treat or ameliorate hypertension and does not anticipate the subject matter claimed in the instant case. As such the references cited above, when considered as a whole do not render claims 1-18 of the instant case unpatentable for obviousness within the meaning of 35 U.S.C. § 103. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103 rejections.

CONCLUSION

The Applicants respectfully submit that the pending claims are in condition for allowance and respectfully request allowance of the same. If there are any questions regarding these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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